THE

INSTITUTE OF CHEMISTRY

OF

GREAT BRITAIN AND IRELAND.

FOUNDED, 1877. INCORPORATED BY ROYAL CHARTER, 1885.

CHEMISTRY AND LIFE

BY

SIR FREDERICK GOWLAND HOPKINS,
M.A., D.Sc., LL.D., D.C.L., F.R.C.P., F.I.C.
(*President of the Royal Society*)

The Fourth Gluckstein Memorial Lecture, 1932

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This, the fourth Gluckstein Memorial Lecture, was delivered before the Institute of Chemistry, at 30, Russell Square, London, W.C.1, on Friday, 16th December, 1932,—Dr. G. C. Clayton, C.B.E., M.P., President, in the Chair.

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CHEMISTRY AND LIFE

I WOULD like first to express my thanks to the Officers and Council of this Institute for entrusting me with the delivery of a Glückstein Memorial Lecture. It is an honour that I appreciate. My vocation and the limitations it involves make it difficult for me, however, to follow the tradition justly established for these lectures. My predecessors have dealt with practical affairs while what I am to say may seem to take you quite away from these. It is my belief, however, that he whom these lectures commemorate, being a man of much imagination, would himself have seen the significance of the line of scientific progress with which I am to deal.

The title of my lecture is an ambitious one, and I am sure you will understand that the field of thought and endeavour to which it would seem to apply—the field of modern biochemistry—must, in a single lecture, be very superficially, or, alternatively, very partially surveyed. It would be relatively easy perhaps to deal under such a title with generalities, and speak of Chemistry and Life from a quasi-philosophical standpoint; but I have thought that to avoid too great a departure from the tradition just mentioned it would be more justifiable to deal with actualities: with methods and experimental results.

It will not, however, be within my power to do more than illustrate by a few examples, and a little discussion, the degree of success which the application of chemical methods to the phenomena of life is just now achieving, while making a brief personal appraisement of the present status and outlook of biochemistry as a branch of experimental enquiry.

Perhaps my chief wish as I address you is that you will agree with the view that living systems should sometimes occupy the thought of every chemist; even if, for good reasons, he is content to leave practical dealings with them to those who are labelled as biochemists. I wish this for a reason which I will try to make clear.

Organic chemistry at its birth was closely concerned with the nature of plant and animal products, but its own great and inevitable development, and especially the growth of the great art of synthesis, and the enormous field for investigation of artificial products which this provided, led chemical thought, for two generations at least, away from the problems of what we now know as biochemistry. The attainment of our present knowledge of molecular structure and all that it stands for is surely one of the greatest triumphs of the application of inductive and deductive thought to experimental data. Progress in that knowledge must continue, but it will not be inhibited if the attention of organic chemists is turned once more to natural products in particular. Indeed it is a matter for much satisfaction to realise that the minds of many among the most distinguished of chemists are just now already so orientated. I will only remind you of the brilliant work done in recent years by Willstätter, Robinson, Howarth, Windaus and others. I am to ask you, however, to think less of biological products themselves than of the changes they undergo during life.

For sound and ample reasons, organic and physical chemists, when engaged in studies of kinetics, simplify, so far as possible, the conditions of experiment, so that their conclusions may be clear and definite. They are accustomed to deal in the main with relatively simple systems. Is it not well, however, that they should bear in mind that chemical systems exist, and have existed ever since living organisms appeared in the world, in which the exact co-ordination in time and space of a multitude of reactions is an essential and indispensible condition? Ultimately the factors and conditions which maintain a high degree of organisation among large groups of reactions must be as much the field of chemical study as the kinetics of simpler systems. Success in illuminating the problems of complex organisation may well prove in the future to be among the greatest fruits of chemical thought and endeavour. That is why I think all chemists should sometimes turn their thoughts to living organisms.

As I have remarked, it is a matter for great satisfaction that distinguished chemists are now engaged upon intensive studies of plant and animal products; but if chemistry is to provide the help that biology so urgently needs it must approach living organisms not as chemical stores but as seats of chemical events! I shall in this Address dwell chiefly on the dynamic side of biochemistry.

Two historical criticisms have been made concerning attempts to apply chemical studies to the dynamics of living organisms. The first is involved in the more ancient assertion, that all such attempts must be futile because chemical methods at the very moment of their application must convert the living into the dead. The second is still current, and comes from philosophy. It claims that the results of such studies have inherent futility, since only those properties which emerge from the constitution of the organism as a whole possess biological reality. The results of chemical studies, it is urged, may have chemical interest, and the sanction of practical utility, but can tell us nothing about Life as an organised reality.

It is part of my purpose to remind you that the first objection can be met, and is being met; the view involved in the second objection is becoming more and more tenuous, I think, as chemical studies progress.

Any discussion of "Chemistry and Life" ought perhaps to begin with reference to photosynthesis in the green plant, since that process provides the energy for the dynamic activities of the great majority of organisms which now exist. The knowledge we have of it at present does not, however, well illustrate the particular lines of thought I want you to follow. I propose to deal mainly, though not entirely, with reactions which occur in animal tissues.

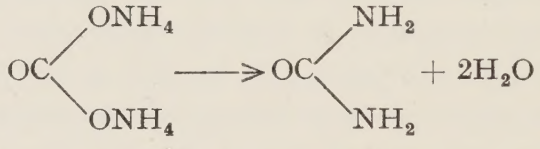
I have just claimed that biochemistry has been able to elude the objection that its methods can only be applied to cells and tissues after those methods themselves have first killed them. I will now recall some of its plans for escaping that dilemma. They comprise not merely the use of preparations in which, though the living structure is frankly destroyed, dynamic events normal to the cell still proceed; though even from these much may be learned that is with certainty applicable to the intact cell. They also comprise methods by which reactions may be quantitatively followed, though occurring in the living cell itself.

I will not speak of metabolic studies carried out on the intact animal, or upon human subjects, though let me say that by taking advantage of various opportunities and by some ingenuity in method we have learned much more than the mere balance sheet of metabolism can tell us. To know that the consumption of so much protein, fat and carbohydrate leads to the excretion of so much urea and so much carbon dioxide tells us, of course, nothing of that succession of complex chemical events intervening

between consumption and excretion, which it is the business of the biochemist to understand. We have, however, managed to learn not a little concerning these, even from studies on the intact and living body; but I am to deal rather with events which occur in individual tissues.

Let me first plunge *in medias res* and ask your attention to a research recently published which illustrates particularly well, I think, the nature of the problems of dynamic biochemistry, the methods open to it, and the kind of success it may hope for. Some of my audience may be aware that I have quite recently quoted this instance, with the same intention, in an Address delivered elsewhere; but it attracts as an illustrative case, and I am tempted to refer to it here.

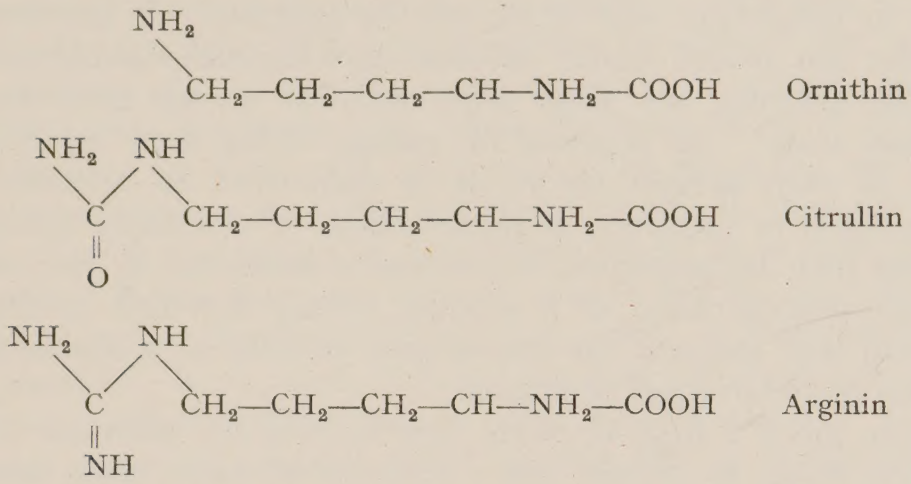
In the research in question the investigator approached on new lines a fundamental problem which for the last sixty years has been the subject of speculation, and no less of experiments which up to a point were informative. The problem was to discover the nature of the final chemical steps which lead to the production in the animal body of that oldest child of synthetic chemistry—urea. That the mammalian liver can convert ammonium carbonate into urea has been many times experimentally proved, and it is equally sure that ammonia and, of course, carbon dioxide, are continuously produced in metabolism; therefore most of us have long been content to believe that urea arises by the direct removal of the elements of water from the molecule of ammonium carbonate on the lines of the simplest of reactions:—



That urea does indeed arise in the liver by a synthesis from ammonia and carbon dioxide remains certain; but the research under reference, brilliantly carried out by Krebs of Freiburg-im-Bresgau has shown that its production is on no such simple lines as those mentioned. It calls for a mechanism involving a most interesting interplay among activated molecules.

In order to make clear to you the essential results of Krebs' research, omitting of necessity most details, I will ask you to

consider the molecular structure of three biological substances: Ornithin, Citrullin and Arginin:—



Note first the structure of ornithin: α-δ-amino valeric acid. In the presence of ammonia and carbon dioxide, and when activated by agencies in the hepatic tissue, ornithin is converted into citrullin which, as an ureido-acid, already carries the carbamide structure. Urea does not arise directly from this, however, —another stage intrudes.

Citrullin takes up another molecule of ammonia (with elimination of water as at the first stage) and the structure of arginin with its guanidin grouping is thus established. Now arginin is the normal substrate for the well-studied and very active hepatic enzyme, arginase, so that at this stage there is clear adjustment between means and end. Under the influence of this enzyme the guanidin group is hydrolised. Urea thereupon splits off from the arginin molecule and ornithin is reproduced. The sequence is then re-established. Urea is thus produced continuously from the ammonia which arises in the deamination of the amino acids of protein, and from the carbon dioxide of metabolic oxidations in general, but on lines which may seem strangely complex. But the complexity is really an aspect of the organisation of chemical events in the liver. The processes involved do not proceed in isolation, and when we know exactly how they are related to other aspects of organisation in the hepatic cells we shall understand why an apparently simple result is so indirectly reached.

Coming now to the question of methods, I must justify my claim that the progress of reactions may be quantitatively followed even when they occur in living tissues. One such

method involves the use of a tissue which, after removal from the body, yields good evidence of survival of life, which is uniform in behaviour, and which can be sampled. A number of samples are placed under suitable and uniform conditions. Individual samples are then dealt with at known intervals on a time scale; the progress of change being first rapidly arrested in each sample before it is submitted to analysis. Some product, or products, of the reaction, or reactions, under study can then be estimated in successive samples. A rise or fall in the concentration of a product during the time of the experiment will indicate the course and velocity of a reaction under the predetermined conditions.

Forgive me if I first illustrate this method by reference to a research which is already old. Some twenty-five years ago Walter Fletcher (now Sir Walter) and I applied such a method to a quantitative study of the production of lactic acid in excised muscles. Muscles provide admirable material for the study of changes in a tissue after removal from the body, because their physiological function, that of contraction upon stimulation, can be so easily observed. In the case of excised muscles therefore we can be sure that our experimental material is in an essentially physiological condition so long as it can be shown to contract normally. The muscles of cold-blooded animals are especially convenient because when undamaged and provided with an adequate supply of oxygen, they remain normal for days after their removal from the animal. The data obtained from them agree in all essentials with those yielded, with somewhat greater experimental difficulties, from all mammalian muscles. In the case of frogs' muscles, which were used by Fletcher and myself, the adequate oxygen supply is secured by placing them in the pure gas. At such a tension the oxygen penetrates the fibres with a velocity sufficient to replace fully the normal supply as provided by the circulation when they are in the body.

In the research under reference, which was of a pioneer nature, we had first to determine that we could work with materials of a perfectly uniform kind so that the condition of a sample, whatever the circumstances of the moment, would represent accurately the condition of the whole in the same circumstances. Such complete uniformity we found in the limb muscles of frogs freshly caught in the same district. We were therefore able to place a series of grouped muscles of known weight under proper and uniform conditions and, by estimating

lactic acid in individual groups after successive known time intervals, we were able to follow any increase or decrease in the concentration of the acid due to reactions occurring in the still living muscles. We had, however, to respect the biological qualities of our material. An injury to a muscle, such as a cut across the fibres, acts, while the tissue is alive, as a strong stimulus to lactic acid production. In preparing our samples for estimations we could not therefore simply chop the muscles up before extraction, or each result would have been much too high. It was necessary in every case to destroy the whole structure, and so throw catalysis out of action, as instantaneously as possible. In our study this end was achieved by rapidly grinding each small individual muscle under ice-cold alcohol. I mention this apparently trivial detail because lack of realisation of the need of such treatment of a still active tissue had before this time led to much confusion in studies of the kind. Since then everybody engaged in similar studies has observed the necessary precaution, though various methods for arresting change instantaneously have been employed.

Of the results we obtained in this early investigation I will here only mention a few. When the oxygen supply is adequate, lactic acid never reaches to more than a minimal concentration either in resting or contracting muscles. In the absence of oxygen on the other hand, the acid accumulates at a rate which in the resting tissue is almost exactly linear, and continues until the stage of *rigor mortis* approaches. The velocity of its formation is greatly increased by contractile activity under anaerobic conditions, the amount of acid produced bearing a definite ratio to the work performed. From a muscle in which lactic acid has accumulated as the result of oxygen want the acid disappears when oxygen is again supplied. The course of this disappearance involves a phenomenon of great interest, but I will postpone reference to it until, a little later, I return to the subject of muscle chemistry. I have so far mentioned only superficial aspects of these happenings, the present reference is in illustration of a biochemical method in which a change is followed as it progresses in a tissue which it would be hypercritical to consider as other than living tissue. The simple principles involved in this method have been followed in a great deal of later work; but with one essential difference in practice. Fletcher and I employed our material in relatively large amounts. Recent years have seen a great development in

micro-methods of analysis. These have been long familiar to all chemists in the case of ordinary combustion analysis. The biochemist in particular has widely extended their range, even to their employment in following the kinetics of reactions and especially in the study of activities in tissues. Their accuracy has always been conscientiously explored, and their use has greatly assisted the progress of dynamic biochemistry. Micro-methods were used in the research on the origin of urea of which I have told you. Another development in technique has been of great importance. We now know well how, by the choice of an exactly adjusted medium, an adequate oxygen supply, and some other physiological adjustments, to secure quite prolonged survival in a variety of tissues after their removal from the body, and thus to follow processes in circumstances essentially normal. Biochemistry has moreover been able to take advantage of the modern technique of tissue culture *in vitro*.

The limited examples I have given will perhaps suffice to justify the claim that chemical methods can demonstrate facts which apply to living systems and not to dead materials alone.

It is sure at the same time that highly significant data are to be obtained by the study of systems isolated from the living tissues. In particular we can follow in suitable aqueous cell-extracts the kinetics of individual reactions, each catalysed by a single enzyme in contact with the substrate to which it is adjusted. Further it is possible to prepare extracts in which associated reactions proceed with a high degree of organisation among themselves. One such case I will mention later.

So much then concerning matters of biochemical technique.

In further illustration of the organised character of chemical reactions as they occur in living cells or tissues I have thought it well to choose, from many possible cases, those fundamental oxidation-reduction processes which are particularly concerned with providing energy for biological activities.

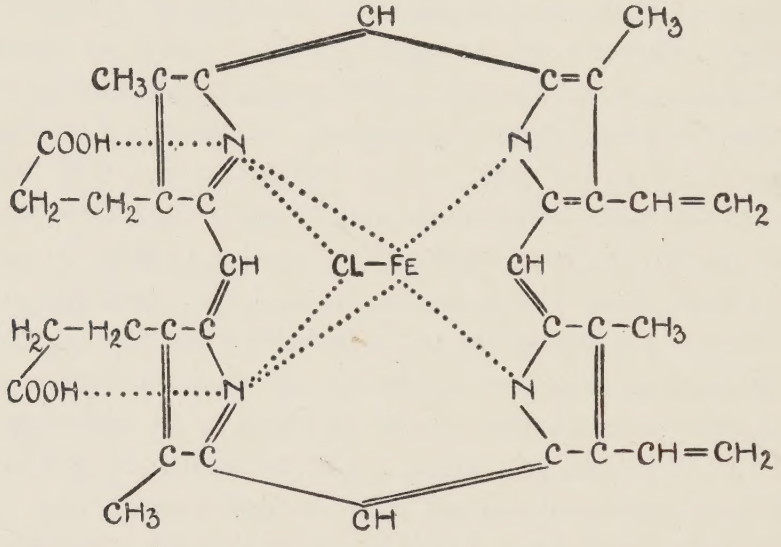
It is noteworthy that much research in the last ten years has shown that biological oxidations conform to the view which Wieland has applied to organic oxidations in general. The molecules to be oxidised are first activated in the sense that constituent hydrogen atoms are made reactive and capable of ready transference to oxygen. In nearly all cases, however, oxidations in the living cell call for activation of molecular oxygen as well as activation of the substrate molecules. The total process involves therefore two distinct types of catalytic

activity, or, in other words, it calls for the influence of two kinds of enzyme. We now speak of those enzymes which, in the sense just mentioned, activate substrates, as dehydrogenases (or dehydrases) and of those which activate the oxygen as oxidases. The former are highly specific in their action, each being adjusted as a catalyst to the activation of one type of molecule alone. Since many and very diverse substances are oxidised in living tissues a great number of dehydrogenases therefore exist, and the activity of several has been carefully studied. In quite brief illustration of this kind of activity I will refer to two cases. An enzyme which controls the first stage in the biological breakdown of succinic acid can be separated from many tissues. When in contact with this "succinic dehydrogenase" a molecule of the acid becomes so activated that in the presence of active oxygen it is converted into fumaric acid; two atoms of hydrogen being transferred to oxygen, $COOH.CH_2.CH_2.COOH \rightarrow COOH.CH:CH.COOH + H_2 \rightarrow$. Biologically activated oxygen, be it noted, has no influence upon succinic acid in the absence of the dehydrogenase. That the action of this enzyme is especially concerned with the mobilisation of hydrogen and not with the activation of oxygen is proved by the significant fact that under its influence succinic acid is readily oxidised to fumaric acid in the complete absence of oxygen, so long only as some easily reducible substance, or (to use a term which has become customary), any suitable hydrogen "acceptor" is present simultaneously to take the place of oxygen. The second case I will mention is that of a purin dehydrogenase which with high efficiency promotes the oxidation of hypoxanthin and xanthin to uric acid. You will recall that these purin bases, like succinic acid, are highly resistant to oxidation by laboratory methods; yet all are readily oxidised under the influence of this biological catalyst. I mention the case of the purin oxidation as differing in two respects from my first example. The molecule of xanthin when activated must associate itself with a water molecule, and that of hypoxanthin with two, before the hydrogen transfer occurs. It is the hydrogen of water which in this case is transferred to oxygen or other hydrogen acceptor, and the oxygen of water which appears in the molecule of the resulting uric acid. A second difference is that in the case of the purin system the activation of molecular oxygen is for some unknown reason unnecessary, or otherwise the catalyst as isolated can exert two functions. In this, the case is quite exceptional however. Many

dehydrogenase activities have been studied, and most are proved to call for the simultaneous activation of oxygen by a separate agency before the oxidation of the substrate is achieved.

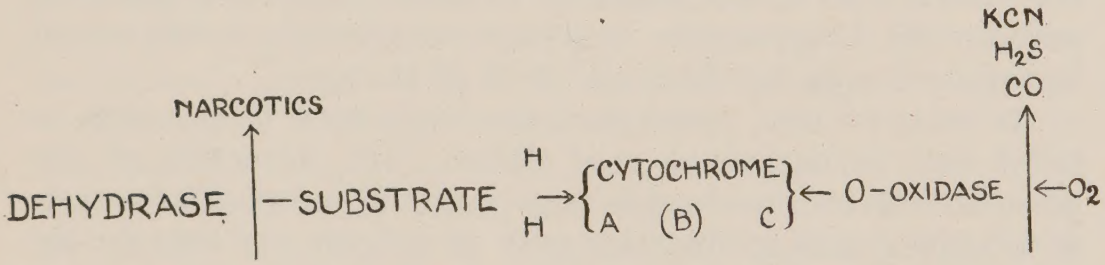
The circumstance that the molecules of the substances to be oxidised have themselves to be specifically activated before oxygen, even when biologically activated, attacks them, prevents indiscriminate oxidations in the cell. This is again an aspect of biochemical organisation.

Especially noteworthy are the mechanisms which bring molecular oxygen into relation with the molecules to be oxidised. In making reference to these I must first remind you of that remarkable group of iron-pyrrol derivatives which play a variety of parts in living systems. As you know, a pyrrol nucleus is present alike in chlorophyll and haemoglobin and is associated with iron in the latter; but this same association is found in several of the catalytic agents in the cell. The structure, while remaining fundamentally the same, is modified in detail when the substances containing it subserve different purposes. As a typical example of the group I will ask you to recall the accepted structural formula of *haematin* which is familiar as a derivative of blood pigment.



You will observe the four pyrrol rings which are almost certainly symmetrically arranged as shown. The side chain groupings vary in different members of this class of compound. When from any of these the atom of iron is removed it yields a *porphyrin ;* when, on the other hand, the iron-pyrrol grouping is linked with protein or one of certain other nitrogenous compounds it yields a *haemochromogen.*

The *cytochrome* system of Keilin consists of three substances of the haemochromogen type. One of the three is the most important, and I will speak of cytochrome in the singular as referring to this substance. It is widely distributed biologically. Its characteristic spectrum can, for instance, be demonstrated by the microspectroscope alike in living yeast cells and in muscle fibres, and indeed in most living cells and tissues. Cytochrome is susceptible under defined conditions of reversible oxidation and reduction, with corresponding changes in the valency of its constituent iron. It is easy, by means of the spectroscope, to distinguish the spectrum of its reduced from that of its oxidised form, and the change can be observed in the still living tissue. If, for instance, a tissue be deprived of oxygen, it becomes obvious from the change of spectrum that systems in the tissue reduce the oxidised form. If on the other hand the reducing systems are inhibited, as they can be by certain narcotics, the cytochrome is seen to become and to remain oxidised. Reduced cytochrome, however, is not oxidised by molecular oxygen. An activating enzyme functions here; an oxidase. The influence of this latter catalyst is entirely inhibited by minute concentrations of a cyanide, and in presence of this the cytochrome can be seen to remain reduced.



By taking advantage of these properties it is easy to see these changes in undamaged and still living cells.

Without considering other details you will see that the association of cytochrome with the oxidase provides the mechanism whereby the hydrogen atoms mobilised by various dehydrogenases are finally oxidised. Such hydrogen reduces the cytochrome, which is then again oxidised by oxygen activated by the oxidase. The whole process is unified and continuous. Here once more we have in this sequence an aspect of chemical organisation in living tissues. There is, I may add, at least one other alternative path for the transport of hydrogen to oxygen which I will mention shortly.

To illustrate further aspects of organisation let me return to active muscle. The chemical events associated with contractile activity have wide biological bearings for a motile response to a stimulus is, of course, highly characteristic of living organisms. The known facts concerning these events are complex, and it is with regret that I must refrain from discussing in detail the interesting experimental evidence which has provided them.

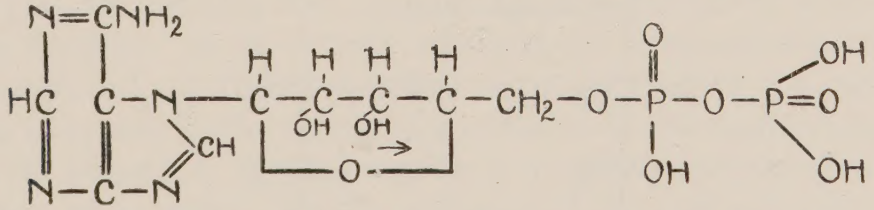
The source from which the lactic acid arises in muscle is its store of glycogen. I have already said that when the acid has accumulated in a surviving muscle as the result of oxygen lack it is locally removed from the fibres when oxygen is again supplied. Now a truly remarkable circumstance is this, that of the lactic acid which thus disappears only about one-fifth, at most, is oxidised; the rest is resynthesised into the glycogen from which it arose. From this well-proved fact and from much other evidence we have come to realise that the events associated with the actual contraction of a muscle as it occurs normally in the body are anaerobic. The oxidations, which are the *ultimate* source of energy for the work done, occur immediately after the contraction, during what is now generally known as the recovery period. During the period of contraction events occur of which the formation of lactic acid from carbohydrate is one. During the recovery period the muscle is restored to its *status quo ante*, save for the disappearance of such of its glycogen as has served to supply energy for the whole cycle of change.

It must be next noted that the breakdown of glycogen to lactic acid is not simple and direct. The formation of the phosphoric ester of a hexose is an essential intermediate stage. It is while in this combination with phosphoric acid that the six carbon sugar derived from the glycogen is split into compounds with three carbon atoms, which are the immediate precursors of the lactic acid. One of these at least, if not the only one, is methyl glyoxal, of which a word in a moment. That phosphoric esters play a most important part in carbohydrate metabolism, and perhaps in other metabolic events, has grown more and more sure during the last decade. It is indeed characteristic of current progress that many of the permanent constituents of living cells which we had tended to view as static, and of merely structural importance, are proving to have dynamic functions.

It was natural, when it was first shown that the sudden appearance of lactic acid in muscle is always associated with anaerobic contraction, to assume not only that the energy of contraction

was derived from this form of carbohydrate breakdown, but that the appearance of an adequate concentration of acid in the muscle fibres might in some way be the efficient cause of contraction. This relatively simple view we have lately had to discard. It has been shown that a muscle may be so treated that carbohydrate breakdown, and therefore lactic acid formation, becomes entirely inhibited, and yet for sensible periods its contractility remains. This striking result occurs when the muscle is poisoned with iodoacetic acid. We might be tempted to reject evidence derived from a poisoned tissue, but it has led to the discovery that we are to look to quite another type of constituent as the immediate (not the ultimate) source of energy for contraction. This energy comes from the hydrolytic breakdown of creatin phosphate, a substance which has become known as phosphagen. Creatin has been familiar of course as a constituent of muscle since the days of Liebig. To-day we have learnt that it is yet another apparently static constituent which in reality serves a dynamic function. As a case of hydrolytic breakdown the decomposition of creatin phosphate yields a relatively large amount of energy, 150 calories for each gram of phosphoric acid liberated, a figure which fits well into the energy balance sheet of the muscle when this is duly determined. Now while the breakdown of phosphagen is associated with contraction this substance is resynthesised, like part of the lactic acid, during the recovery period. This is an essential factor in "recovery."

The facts I shall now add to this story, facts very recently won, reveal a complexity which may somewhat tax your belief since you are not now to hear the evidence upon which the facts are based. It seems to be clear that the endothermic process represented by the resynthesis of creatin phosphate during the post-contractile recovery is itself supported by the exothermic breakdown of yet another muscle constituent, namely adenyl-pyrophosphate, a substance of much biological significance.



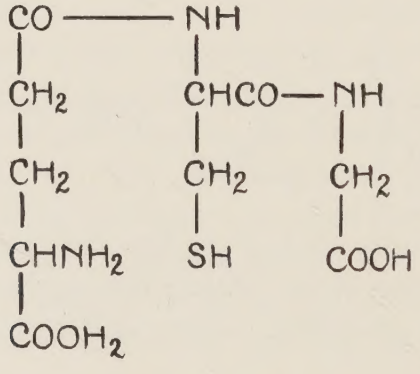
Finally, it appears that it is the energy for the resynthesis of this last substance alone which the carbohydrate breakdown in muscle directly provides. You will note that part at least

of the lactic acid produced, the creatin phosphate and the adenylpyrophosphate, undergo reversible changes in due and proper sequence; they are all, as it were, part of the machinery of the muscle. Its fuel is carbohydrate. It is surely striking that once again we find a given biological end, in this case the supply of energy for (and, in some way, the determination of) a muscle contraction, calls for so remarkable a sequence of organised chemical events. The mechanism whereby energy is transferred from exothermic to endothermic processes in the chemical organisation of tissues is often difficult to understand. In the case of these associated reactions in muscle, since phosphoric acid ions play a prominent part throughout, it is nearly sure that the acid is the common constituent which secures coupling of the reactions.

We owe many of the fundamental facts of muscle chemistry to the highly important researches of Otto Meyerhof and his colleagues at Heidelberg; but from the time that intensive chemical studies of this tissue began they have been supported and controlled by the brilliant thermal studies of A. V. Hill and his school.

Allow me at this point just one further illustration of organisation among chemical events in the tissues which is, I think, instructive.

I mentioned earlier that there is another known path besides the cytochrome path which, so to speak, conducts activated hydrogen to activated oxygen. This depends upon the reversible relation which holds between sulphydryl compounds and the corresponding disulphide compounds which result from this oxidation. Several years ago I isolated from various tissues a substance to which I gave the name glutathione, which is now known to be, in its reduced condition, a tripeptid containing glutamic acid, glycine, and cystein, with the following structural formula:—



The substance is widely distributed in living tissues. I have myself isolated it in pure crystalline form from yeast and various animal tissues, including so highly specialised a tissue as the transparent optical lens. It has unusual properties as a peptid, but these I must not stop to discuss; the only point of importance here is that in this combination the cystein structure as a whole is stabilised, whereas the thiol group is oxidisable in the living cell, yielding the disulphide form of the peptid. The latter, on the other hand, is, like cytochrome, reducible by certain dehydrogenase activities. These opposed processes of oxidation and reduction, when the cell is alive, tend to reach a dynamic equilibrium, which means that hydrogen is continuously transferred to oxygen by this path. As a rule the velocities of oxidation and reduction are so adjusted that the glutathione is maintained mainly in the reduced form. Now much recent experimental work seems to have shown that in this form glutathione exercises quite specific functions. One such relates it with the story of muscle which has been before you. I mentioned just now that one, if not the only, immediate precursor of lactic acid, in the course of its formation from carbohydrate, is methyl glyoxal: $CH_3.CO.COH + H_2O \rightarrow CH_3.CHOH.COOH$. This final step is catalysed by a specific enzyme, *glyoxalase*, for the activity of which, however, the presence of reduced glutathione as a co-agent is essential (Lohmann). The properties of glutathione are therefore such that, though as a carrier for transported hydrogen it continually suffers oxidation and reduction, yet so long as a concentration of the reduced form is maintained, it at the same time exercises essential functions quite peculiar to itself. Such a linkage between two apparently unrelated processes is surely interesting as a specially significant illustration of chemical organisation in the tissues.

In order to emphasise a consideration which seems to me to lend significance to all the facts I have put before you I will ask you to consider the case of muscle chemistry even yet a little further. It is a truly remarkable circumstance that all, or nearly all, of those chemical sequences which we have seen to be involved in the chemical dynamics of the contractile tissue can be observed in progress in a properly prepared aqueous extract of muscle. In the absence of all cell structure these reactions progress, and to attain the end result as observed they must progress in due order. These involve syntheses and no less a coupling of different reactions, energy being transferred

from one process to another. If we enquire how chemical events can be so organised in a solution which, though of course colloidal, is otherwise homogenous, the answer I am sure is that it is because the colloidal catalysts derived from the original tissue, of which many are found in the extract, are highly specific in their individual activities. I have mentioned enzymes only incidentally in the course of my remarks, and it is impossible to discuss their nature here. It is sufficient to remember that high specialisation in their individual catalytic powers especially characterises these biological agents. An enzyme, though a highly efficient catalyst, activates either one kind of molecule alone, or at most two or three very closely related molecules. In some few cases its influence may extend to a limited range among substances of the same type; but specificity in action is the essential stamp of an enzyme. Now I would not have you think because a great number of individual enzymes have been separated from animal tissues, fresh ones being still repeatedly described, that this means the isolated entities are in any sense artifacts. I think you should rather believe that realisation of the circumstance that a living cell contains many highly specialised catalysts, each one necessary for the progress of some individual reaction, will greatly help towards an understanding of that high degree of organisation displayed by reactions within the cell. None of them proceed uncatalysed, and the velocity of each one is controlled by the concentration of its specific catalyst. You should also remember, moreover, that highly specific catalysts determine just what particular substances, rather than any others, shall undergo change. They have selective powers. Further, any given molecule may suffer one line of change on meeting a particular catalyst, while if it meet a catalyst or catalytic system, different but also adjusted to it, the molecule may suffer quite another change. Specific catalysts have directive powers. I have elsewhere endeavoured to develop this theme, but cannot do so here. If, however, you can spare thought to the matter, I think you will come to the conclusion that the activities of highly specific catalysts distributed in a colloidal system like the living cell may by themselves induce a high degree of organisation in respect of velocities and sequences among the reactions which they control in that system. Enzyme control is indeed a fundamental aspect of the chemistry of life.

The biochemist, when pursuing his science for its own sake, rather than for immediate practical aims, has to realise that

each time he demonstrates a new activity in a living tissue or cell his discovery can only reach its full biological significance when he can see how it is related to the organised activities of the whole system. Ability to do this is of course very limited at present, and can only gradually increase with the increase of knowledge.

It is surely because of the necessity for their presence at some nodal point or other in the intricate machinery of chemical organisation in the animal body that such agencies as hormones and vitamins reach their importance. Thinking of the latter, it is a task still ahead to decide how the presence or absence of the fraction of a milligram of a specific substance in the day's intake of an animal can ultimately determine between life or death. It is, however, satisfying to all interested in biochemistry to realise how rapidly we are just now progressing towards a full knowledge of the constitution of vitamins. The same may be said of hormones. Upon this knowledge our ability to determine precisely how these exert their influence in such minute amounts will be based.

I have all this time been dealing in the main with facts which apply in particular to the tissues of vertebrate animals. It is clear that a full understanding of the relation between chemistry and life must have a broader basis than this. By the study of invertebrate animals, of the green plant, of the lower fungi and of micro-organisms in general, we are learning what aspects of the relation are fundamental and essential and what are special. Only so moreover can we learn about the extraordinarily interesting chemical modifications which are associated with, and underlie, morphological modifications—the chemistry of species.

Lest we should here forget the infinite variety of the processes associated with life I will allow myself, before concluding, a very brief reference to micro-organisms; to bacteria. Ordinary so-called heterotrophic bacteria which cannot dispense with organic carbon compounds in their nutritive medium display many activities in common with animal cells. As you will know, a very large literature deals with studies of their enzyme systems, and with the great variety of reactions which they control; studies which have yielded results of the widest interest. If, however, we would arrive at a due estimate of all the potentialities inherent in Life (using the word as we well understand it, though it is so difficult to define with precision), we must, you will agree, remember always the autotrophic bacteria which

deal with inorganic materials alone. They obtain their energy by oxidising various inorganic materials: hydrogen, sulphur, iron, ammonia or nitrites. Provided with such energy, they carry out the remarkable syntheses which lead to their growth and start by rivalling the green plant in the endothermic reduction of CO_2, though without the aid of solar energy. Such organisms are of the greatest interest, because their activities seem to carry us nearer than those of other organisms to the beginnings of life; perhaps to the days before evolution had established the chlorophyll function of the green plant, that great success of Nature. These autotrophic bacteria suffer however from the very low efficiency which characterises their method of obtaining energy, and it would seem as though they are the survivors from an unsuccessful evolutionary effort. Because of the interest which cannot but be felt in all the chemical adjustments which are associated with the steps and stages in the evolution of living forms, I will close by calling your attention to a group of autotrophic bacteria recently studied which have gone a step farther than others towards success in obtaining cheaper energy. I allude to the purple sulphur bacteria, a group which still relies upon the oxidation of sulphur, but which, having developed an adequate pigment for the purpose, can trap and employ radiant energy as well. A careful study of their metabolism has shown that the following reaction represents the process by which the preliminary reduction of CO_2 to formic aldehyde occurs. But these particular organisms require sunlight for growth because the reaction represents a photosynthetic process.

$$H_2S + 2H_2O + 2CO_2 = 2CH_2O + H_2SO_4$$

Speaking in parables, we may say that Nature has made many experiments, some successful and others unsuccessful, in developing the forms of living organisms; while in relation with these she has made many chemical experiments also with varying success. In biology, success means nice adjustment between the equipment of an organism and the opportunities its environment provides.

Influenced perhaps by the title chosen for my lecture I have dealt with matters which seem remote from practice, though they may be nearer to it than we think. I might perhaps have dealt rather with the practical applications of biochemistry which are becoming numerous enough. I would indeed advise any young chemist when deciding upon a career to bear their

possibilities in mind. In normal times at least, applied biochemistry offers promising paths. Even those, however, whose concern is with the more practical aspects of the subject must seek for an understanding of the intimate chemical behaviour of living systems, since this alone will give meaning to biochemical data, in whatever connexion they are sought.

When the chemist's mind turns to consider our present inadequate knowledge of the complexities of living things it can hardly fail to be humbled. You have had before you, for instance, certain facts concerning chemical events in active muscles which I think you will agree are significant. When, however, we try to picture the orderly sequence of these chemical events as they must proceed in the instantaneous response of our muscles in reflex actions, or, say, in the muscles which keep an insect's wing beating very many times in a second, our imagination is strained. We know that the dynamic chemical phenomena reveal an essential aspect of life; but we are led to feel that other aspects may lie deeper than these. In any description of the physical basis of life, however, they must always be of fundamental importance; and though our present knowledge of them is but small, it is growing rapidly, and we are justified to-day in the belief that it is progressing on right and profitable lines.

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